Thesis of Master of Science

Effects of High Intensity Interval Training on Muscle Function and Body Composition in Prostate Cancer Patients Receiving Androgen Deprivation Therapy

고강도 인터벌 운동이 안드로겐 박탈치료를 받는
전립선암 환자에서 근 기능 및 신체조성에 미치는 영향

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Effects of High Intensity Interval Training on Muscle Function and Body Composition in Prostate Cancer Patients Receiving Androgen Deprivation Therapy

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ABSTRACT

Introduction:

Majority of patients with prostate cancer experience negative changes in body composition and physical function after receiving androgen deprivation therapy. These increase a risk to contract metabolic syndrome and chronic diseases which consequentially decrease the patients' health-related quality of life and increase mortality. As exercise has been considered as a key solution to ameliorate these adverse effects, numerous exercise intervention studies have been conducted. However, there is a lack of research to clarify the effect of high-intensity interval training that may be more effective and more necessary for prostate cancer patients. The purpose of this study is to define the effect of high-intensity interval training compared to moderate-intensity continuous training in a change of body composition and physical performance focusing on muscle function in patients with prostate cancer.

Methods:

Twenty-four patients who met study criteria were recruited and allocated to either high-intensity interval training group (n=12) or moderate-intensity continuous group (n=12). Before and after participating 12 weeks of the exercise program, all patients were measured (1) body composition and bone mineral density, (2) muscle strength and endurance, (3) self-reported questionnaires,

(4) physical fitness. The type of exercise in both groups was combined exercise using an elastic band. High-intensity interval training group exercised twice a week targeting 75-85% of individual heart rate max and 14 to 17 rated perceived exertion (RPE). Patients in moderate-intensity continuous training group received exercise education at the beginning and in the middle of the intervention in order to do walking and resistance exercise in moderate intensity targeting 12 to 15 RPE at home. The amount of the exercise was monitored by pedometer record and daily log file in this group.

Results:

Of the twenty four patients, eighteen patients (High-intensity interval training group; n=9, Moderate-intensity continuous training group; n=9) completed the exercise program and six patients failed for various reasons (body pain 2, hospital movement 2, personal reason 2). Following 12 weeks of the high-intensity interval training program, there was significant difference of interaction between group and time in upper body muscle endurance measured by arm curl test(p=.019), lower body muscle endurance measured by isokinetic dynamometer at angular velocity of 180° /sec (p=.035) and chair stand test(p=.012). Also, FACT-P which is a questionnaire to evaluate the quality of life was improved by over 10% in high-intensity interval training group, a significant difference in interaction (p=.011). However, there was no significant result found in body composition and bone mineral density, muscle strength.

Conclusion:

12 weeks of high−intensity interval training clearly demonstrated a beneficial effect on upper and lower body muscle endurance and quality of life in prostate cancer patients who have been receiving androgen deprivation therapy. The other outcomes were similar to moderate−intensity continuous training. Therefore, high−intensity interval training may be a time−efficient exercise strategy. The further study is needed to verify the exercise program to improve body composition and certain aspects of the health of prostate cancer patients.

Keywords : High−intensity interval training, Prostate cancer, Androgen deprivation therapy, Body composition, Muscle function

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Ⅰ. Introduction

1. Significance of the Study

Cancer is a serious disease associated with substantial medical and economic burden on society(Torre, Siegel, Ward, Jemal, & Biomarkers, 2016). About 14.1 million new cases and 8.2 million deaths were estimated worldwide in 2012 based on data collected by the International Agency for Research on Cancer(IARC)(Ferlay et al., 2012).The incidence rate expected to rise by 70% over the next two decades due to a change in lifestyle and aging in modern society(Stewart & Wild, 2014). According to Korean national statistics, a total of 224,177 new cases and 73,759 deaths were reported in 2012 (Ministry of Health and Welfare, 2015). Cancer is Korean national burden considering that it is the one top leading cause of death and medical expenses are also 4.2 trillion won per year (Health Insurance Center, 2014).

Especially, prostate cancer shows the highest number of new cases in males in a western country(R. L. Siegel, Miller, & Jemal, 2016). Approximately 1.2 million people diagnosis prostate cancer and 0.3 million people died through cancer every year in America(Bray et al., 2018). In Korea, the incidence rate of prostate cancer is the fifth highest; however, the annual average rate of increases is rising rapidly. Korean National Cancer Center reported that new cases increased 6.7 times in 2015 compared to 1999 (Ministry of Health and Welfare, 2015). Prostate cancer is characterized by a high survival rate, more than 90% of patients survive at least 15 years after their diagnosis(Freedland & Moul, 2007). Based on this data, we can estimate that the numbers of prostate cancer survivors is expected to rise sharply. Although treatments for cancer include surgery, radiotherapy, chemotherapy, and hormone therapy successfully increase the survivor rates, adverse effects after treatment remains a major concern for the cancer patients.

Androgen deprivation therapy is one of the common treatments of prostate cancer that slows tumor progression, however, it accompanied a range of adverse effects(Sharifi, Gulley, & Dahut, 2005). It accelerates the decline in bone mineral density by up to 10-fold(R. L. Siegel et al., 2016). Also, androgen deprivation therapy results in increased body fat up to 9% to 11% and decreased lean mass 2% to 4% of initiation of treatment(Gardner, Livingston, & Fraser, 2014). In the cross-sectional study, the prostate cancer patients were significantly lower in upper- and lower-body muscle strength than healthy age-matched controls, in addition to physical performance(D. Galvao et al., 2009a). Moreover, it causes an imbalance of hormones and makes patients experience metabolic dysfunction which has a high potential to occur metabolic syndrome and diabetes that could lead to secondary mortality(Taylor, Canfield, & Du, 2009). Also, sexual dysfunction, hot flashes, and even in cognitive and mood changes have been reported(Bolla et al., 2009). To migrate these effects, many evidences suggest exercise as a key solution (Bourke et al., 2016; D. A. Galvao, Taaffe, Spry, Joseph, & Newton, 2010; Keogh, MacLeod, & management, 2012).

During the past few years, physical activities or exercise have shown to be safe, feasible, and effective in cancer patients. A recent study has been reported that prostate cancer patients who did vigorous activity weekly were shown 49% reduction in death from not only cancer but also from all causes(Kenfield, Stampfer, Giovannucci, & Chan, 2011). Uth et al. (2014) reported that patients performed football for 12 weeks with 84.6% of maximal heart rate improved lean body mass and muscle strength compared with usual care in men with prostate cancer. Exercise guidelines for prostate cancer recommend moderate to high intensity of exercise, but studies on the effect of high intensity exercise are not much conducted. Especially, none of the studies investigate high-intensity interval training which is one of high intensity exercises. Therefore, this study has been conducted to investigate the effect of high-intensity interval training on muscle function and body composition in prostate cancer patients receiving androgen deprivation therapy.

2. Purpose of the Study

This study was aimed to investigate the effects of high-intensity interval training on muscle function and body composition in prostate cancer patients receiving androgen deprivation therapy.

3. Research Hypothesis

To clarify the purpose of this study, the following research hypotheses were set up.

1) 12 weeks of high-intensity interval training would prevent negative changes in body composition and bone mineral density in prostate cancer patients.
2) There would be a difference in the degree of improvement on muscle function of upper and lower body between groups over time.
3) There would be a difference in the degree of improvement on physical performance between groups over time.
4) There would be a difference on self-reported quality of life and physical activity between groups over time.

Ⅱ. Literature Review

1. Cancer and Exercise

Cancer is a disease caused by an uncontrolled division of abnormal cells in a part of the body and divides without stopping and spread into surrounding tissues(Sherr, 1996). Cancer cells may able to interfere with the normal growth of general cells and destroy body immune system that consequently leads patient death(Coussens & Werb, 2002). As a treatment of cancer, surgery, radiotherapy, chemotherapy, and hormone therapy may help to remove cancer tumor or delay its growth(R. Siegel et al., 2012). However, these treatments are highly associated with adverse effects that lead physical, psychological and behavioral changes(Stefani, Galanti, Klika, & Kinesiology, 2017)(Table1). Surgery induces muscle damage on the surgical site and limits its function. For example, proctectomy or hysterectomy patients often suffer from urinary incontinence and sexual dysfunction due to damage on pelvic floor muscle tissues (Bessaoud et al., 2016; Chen, Lin, Wang, & Lee, 2002). Radiation and chemotherapy are known as negatively effects on depression and cancer-related fatigue in breast, lung, pancreatic, brain cancer patients(Blázquez & Cruzado, 2016; Jereczek-Fossa, Marsiglia, & Orecchia, 2002). And hormone therapy makes metabolic dysfunction which increases the patient mortality by secondary causes(Morote et al., 2015).

Table 1. Late and long-term effects of cancer treatment impact on physical, psychological and behavioral changes (Stefani et al., 2017)

Cancer Treatment	Physical Changes	Psychological and Behavioral Changes
Surgery Radiation Chemotherapy Immunotherapy Hormone Therapy Steroid Therapy	↓ pulmonary function	↓ decreased exercise/physical activity
	↓ cardiac function	↑ physical symptoms and pain
	↓ muscle mass	↑ depression
	↑ fat mass	↓ cognitive function
	↓ Decreased muscle strength/power	↓ Quality of life (multiple domains)
	↑ inflammation	
	↓ immune function	
	↓ bone health	
	↑ trauma and scarring	
	↑ lymphedema	

As abundant evidences show that exercise is a safety method to turnover negative changes of cancer patients, American College of Sports Medicine(ACSM) issue exercise guidelines for cancer survivors by cancer type(Stefani et al., 2017)(Table 2). Generally, aerobic exercise is recommended for 150 minutes per week of moderate intensity exercise or 75 minutes of vigorous intensity activity per week. In the case of resistance exercises, it is recommended to do muscle strengthening exercise at least twice a week focusing on major muscle.

Table 2. The ACSM Exercise Guidelines for Cancer Survivors (Stefani et al., 2017)

	Aerobic	**Resistance**	**Flexibility**
US Physical Activity Guidelines for Americans (PAGA)b	150 min/week of moderate intensity or 75 min/week of vigorous-intensity activity, or an equivalent combination.	Muscle-strengthening activities of at least moderate intensity at least 2 days/week for each major muscle group.	Stretch major muscle groups and tendons on days other activities are performed.
Breast	Follow US PAGA.	Start with supervised program and progress slowly.	Follow US PAGA.
Prostate	Follow US PAGA.	Follow US PAGA.	Follow US PAGA.
Colon	Follow US PAGA.	Follow US PAGA except with stoma, where lower resistance and slower Progression are recommended to avoid herniation.	Follow US PAGA, taking care to avoid excess abdominal pressure if patient has ostomy.
Gynecologic	Morbidly obese women may require additional supervision.	Data on safety and benefits are not available for women with lower limb lymphedema.	Follow US PAGA.

2. Prostate Cancer and Exercise

Prostate cancer is a malignant originating from the prostate site, a male reproductive tract surrounding the urethra(Mohler et al., 2016). The type of tumor can be classified according to the degree of differentiation of the tumor tissue, the size of the tissue, and the characteristics of the cell(Mohler et al., 2016). Until recently, the cause of prostate cancer was not clearly defined, but age, race, family history, obesity, and male hormone are known as risk factors(Bostwick et al., 2004).

To define the cancer grade and stage is important when deciding upon the right type of treatment option. Among the differentiation classifications, Gleason score which usually classified the risk (low risk: 6 or lower, intermediate risk: 7, high risk: 8-10) is the most widely used because of their high reproducibility and predictability(Gleason, Mellinger, & urology, 2002). The prostate cancer stage is commonly classified with TNM. T divided into T1 to T4 according to the degree of cancer spread. T1 and T2 are defined as localized prostate cancer, and T3 and T4 are defined as locally advanced prostate cancer(Izumi et al., 2015). N refers to cancer is present in nearby lymph nodes, NO if not present. M indicates whether there is evidence of cancer metastasis to other areas of the body or not. Prostate cancer patients in stage T1 and T2 usually have given curative treatment such as radical prostatectomy and radiotherapy. And the patient has watchful waiting or hormone therapy after surgery. From stage T3, hormone therapy is conducted as preoperative treatment (Tsukamoto, Masumori, Kunishima, & Kitamura, 2004) (Figure 1).

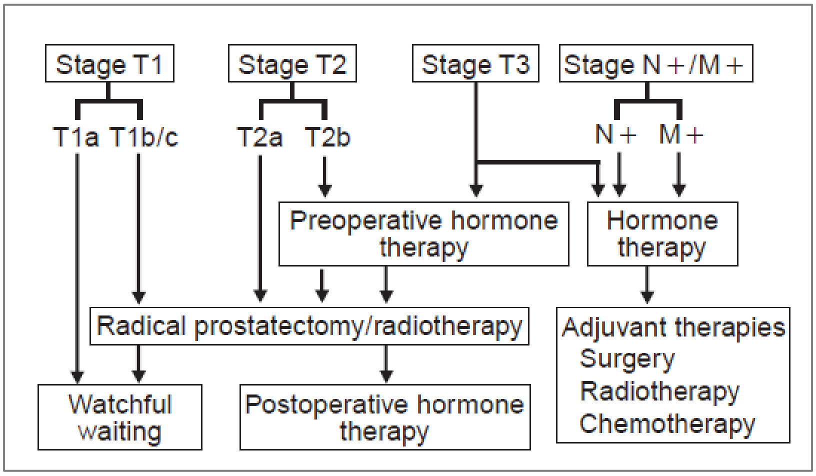

Figure 1. Treatment strategies for prostate cancer by stage (Tsukamoto et al., 2004)

Prostate−specific antigen test, histology, imaging, and other medical technologies have made it possible to screen and diagnose prostate cancer in an early stage. In addition, various treatments developed in surgery, chemotherapy, radiotherapy, and hormone therapy have greatly improved survival rates. However, the patients after cancer treatment undergo adverse effects which cause severe morbidity and a decrement in quality of life.

Depending on the treatment procedure, adverse effects appear in different ways. Accumulating evidence suggests that exercise after cancer treatment may migrate the adverse effects. The adverse effects of each cancer treatment and the effects of exercise on them are as follow.

Surgically, radical prostatectomy is known as inducing stress urinary incontinence which is thought to result of sphincteric insufficiency causing from sphincteric injury or effects on the bladder detrusor muscle(MacDonald, Fink, Huckabay, Monga, & Wilt, 2007). One study reported that 4-31% of patients showed stress urinary incontinence after robotic prostatectomy, 5-34% for laparoscopic prostatectomy, and 7-40% for open radical prostatectomy(Montorsi et al., 2012). Kegel exercises are very common techniques for management of post-prostatectomy incontinence, and various intervention studies relate to pelvic floor muscle training have been proven that progressive pelvic floor muscle training is the key to migrate urine leakage after radical prostatectomy(Park et al., 2018).

The major adverse effects of radiation therapy are known to increase cancer-related fatigue of prostate cancer patients and decrease their quality of life. In the study of Segal et al. (2009) while fatigue in aerobic exercise and resistance exercise group was shown 4.1- to 4.8-point improvement in FACT-F(functional assessment of cancer therapy-fatigue), the usual-care group felt a worsening of fatigue. There is a study that 4.2-point change associated with a 2g/dL increase in hemoglobin after treatment with erythropoietic agents which has a clinically important meaning(Littlewood et al., 2006).

3. Androgen Deprivation Therapy and Exercise

Among the prostate cancer treatment, androgen deprivation therapy is one of the common treatments of prostate cancer that may be used alone or in combination with other therapy depending on the cancer progression of the patients. Because male hormones promote the growth of prostate cancer cells, blocking or suppressing male hormone production can prevent or delay cancer progression. Androgen deprivation therapeutic approaches to disturb the production and/or the action of testosterone include: (1) surgical removal of the testes; (2) using LHRH (luteinizing hormone-releasing hormone) agonists, or LHRH antagonists; (3) inhibiting 5αR (5-alpha-reductase); and (4) blocking binding of DHT (dihydrotestosterone) (Hellerstedt & Pienta, 2002) (Figure 2).

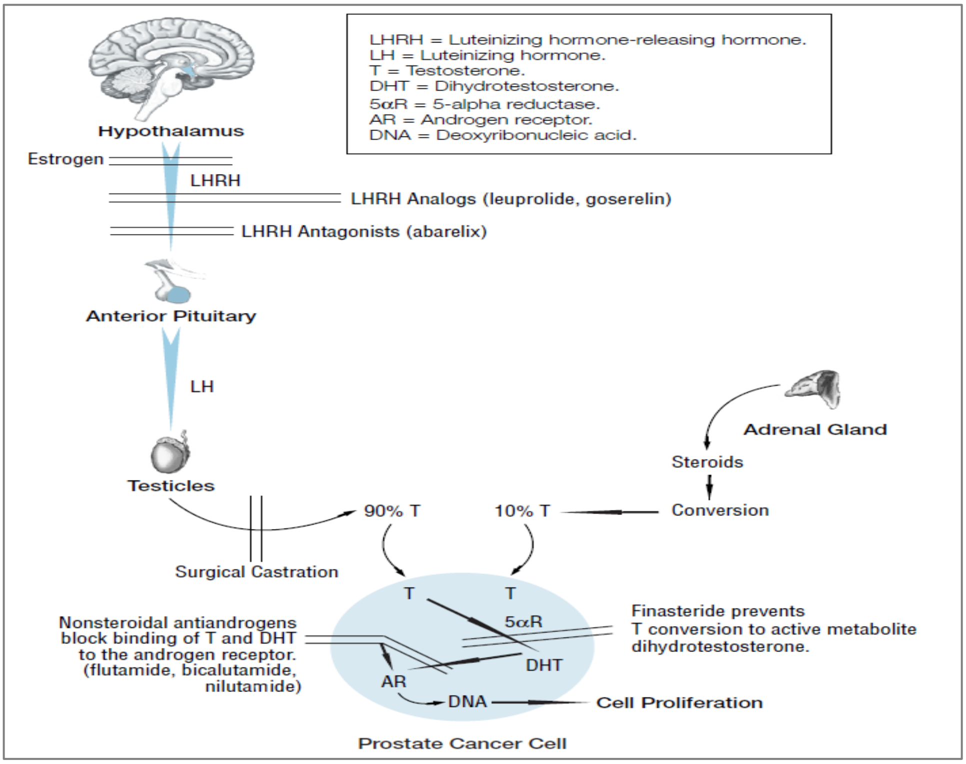

Figure 2. Strategies for androgen deprivation (Hellerstedt & Pienta, 2002)

Androgen deprivation therapy may slow the progression of prostate cancer and reduces overall mortality, however, it accompanied by a various side effects that can be fatal to patient's health. Androgen deprivation therapy causes imbalance of hormones and make patients experience negative changes such as metabolic changes, skeletal complication, sexual dysfunction, hot flashes, and even on cognitive and mood change. Especially, it has a highly positive association with developing metabolic syndrome and diabetes which may be secondary mortality factor in the patients(Dueregger et al., 2014)(Figure 3). All this, as well as sarcopenia and frailty which is highly associated with mobility disorders can be occurred to them(Smith et al., 2012).

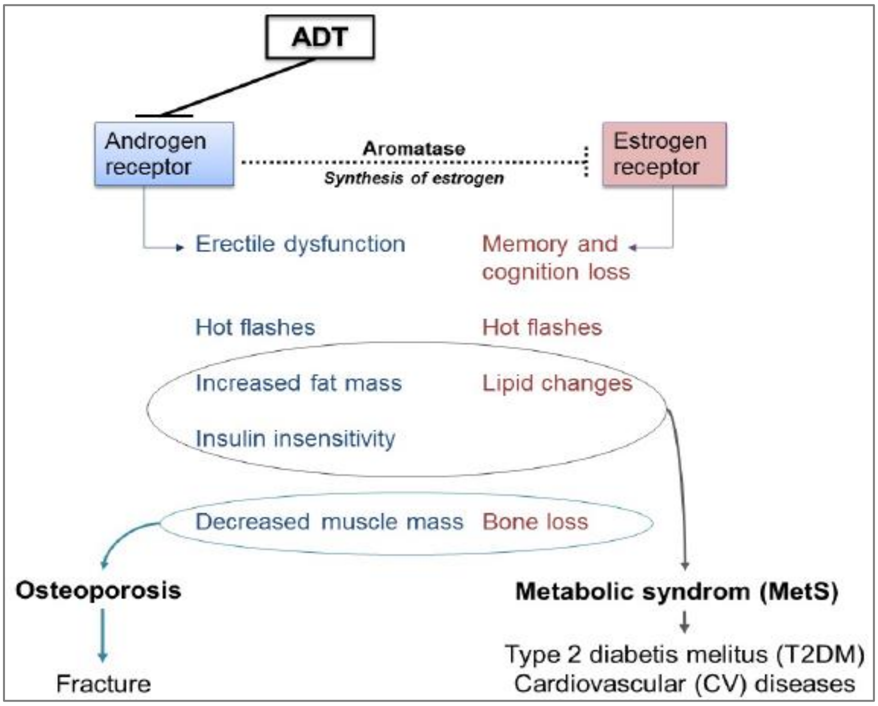

Figure 3. Side effects with androgen deprivation therapy (Dueregger et al., 2014)

To migrate theses adverse effect of androgen deprivation therapy, many irrefutable evidences show that regular exercise is the key solution. Combined resistance and aerobic exercise or resistance exercise alone with moderate intensity has been studied the most so far. D. A. Galvao et al. (2010) analyzed 57 prostate cancer patients who received androgen deprivation therapy by dividing them into combined exercise group and non-exercise group for 12-week. In exercise group, muscular strength, muscular endurance, 6−minute walk, lean body mass, and quality of life were improved. Cormie et al. (2015) compared 63 patients who underwent androgen deprivation therapy for prostate cancer to exercise and non−exercise groups after 3 months of enrollment. Body fat, and abdominal fat, muscle strength, cardiovascular test, and blood markers showed significant differences.

Also, Cormie et al. (2013)evaluated the changes in sexual function after 12 weeks of exercise regimen. 58 patients who received androgen deprivation therapy divided into exercise and non−exercise groups in for prostate cancer. In the pretreatment evaluation, sexual arousal was similarly evaluated between groups. However, in the exercise group after 12 weeks of exercise, sexual desire remained similar to that before the hormone treatment, whereas the non−exercise group showed a significant decrease in sexual desire.

4. High Intensity Interval Training

High−intensity interval training is a method of workout that alternates between short repeated burst of high intense exercise and recovery(Gibala, Little, MacDonald, & Hawley, 2012b). At one time, high intensity interval training was studied as a means to improve the performance of elite athletes. However in recent years, studies have been actively conducted in a range of population from middle age adults with metabolic syndrome to obese people since adaptations such as improvement of VO2peak, high density lipoproteins, PGC−1α, maximal rate of $Ca_{2}+$ reuptake occur significantly with the exercise (Fisher et al., 2015; Weston, Wisløff, & Coombes, 2014a). To improve cardiovascular and metabolic function, person who has variety of diseases including cancer has begun to replace low to moderate intensity exercise with high intensity exercise. Schmitt, Lindner, Reuss-Borst, Holmberg, and Sperlich (2016) compared the effects of 3 weeks high intensity interval training to low−to−moderate intensity exercise on 28 female cancer survivors. High intensity interval training group performed eight times of 1 minute exercise at >95%HR_{peak} with 2 minutes recovery. And the control group performed 75 minutes of exercise at 60% HR_{peak}. As a result, both group similarly improved body composition; cancer related fatigue and quality of life in safety condition.

Ⅲ. Materials and Methods

1. Participants

A prostate cancer patient who has been undertaken androgen deprivation therapy more than three months was voluntarily recruited from Boramae Medical center in Seoul, South Korea. Urologists initially checked for the patients' physical condition and excluded patients who were suspected to have difficulty in participating in this study due to age and serious musculoskeletal, cardiovascular, neurological disorder. Specific exclusion criteria are as follow: i) ≥80 years old, ii) ≥6 metastases lesions or bone metastasis of hip or femur lesion which make behavioral limitations, iii) ≥140 mmHg of systolic blood pressure, but a person who does not take antihypertensive drugs, iv) ≤−2.5 T−score, but a person who does not take a prescription.

Twenty−eight patients were confirmed as being able to participate in the exercise program from the doctors. Among them, four patients were dropped out as they were judged to be inadequate to participate in the program after conducted Physical Activity Readiness Questionnaire from the Health and Exercise Science laboratory in Seoul National University. Twenty−four patients consequently participated in twelve weeks exercise program after fully aware of the objectives and give consent to research. Except for the six patients who were dropped out due to various reasons (body pain, hospital movement, personal reason), data from eighteen patients who completed the program were finally analyzed. This research is approved by the Institutional Review Board of Seoul National University Boramae Medical Center.

2. Study Design

Before the study begins, a literature survey on prostate cancer patients and exercise intervention was conducted. After obtaining the approval from the Institutional Review Board, volunteers were recruited from the hospital. To assess for eligibility, we double checked from the medical center and the exercise center and four out of twenty−eight patients failed the screening test. Twenty−four patients were assigned to each of the following group: High−intensity interval training (HIIT; n=12) group; Moderate−intensity continuous training (MICT; n=12) group. The exercise programs intervened for 12−week; 4−week of adaptation was allowed for patients by doing exercise training with body weight. From week 5 to 8 and week 9 to 12, patients used the green and blue color of the resistance band in order to progressively increase the intensity of exercise. We analyzed pre/posttest data and drop−out data were excluded (Figure 4).

Literature survey

Prostate cancer, adverse effect, exercise program

⇓

IRB approval

Institutional Review Board of Seoul National University Boramae Medical Center

⇓ **Subject recruited (n=28)**

Assessed for eligibility (n=28)

Criteria of age, metastasis, blood pressure, bone mineral density

⇓ **Excluded (n=4)**

Declined to participate (n=4)

Allocation (n=28)

⇓

12-week exercise program (n=28)

High-intensity interval training group (n=12)	Moderate-intensity continuous group (n=12)

⇓ **Drop-out (n=6)**

Body pain (HIIT; n=1, MICT; n=1)

Hospital movement (n=1, n=1)

Personal reason (n=1, n=1)

Data analyzed (n=18)

High-intensity interval training group (n=9)	Moderate-intensity continuous training group (n=9)

Figure 4. Study flow chart for 12-week exercise program

3. Exercise Program

3.1 High-Intensity Interval Training Program

Center based high intensity interval training program consists of 60 minutes in one session twice a week for 12 weeks. The program composed with warm-up and cool-down for 15 minutes each, and high intensity interval training for 30 minutes. Two sets of seven work-out targeting the major muscles of upper and lower body were performed with a one-minute interval (squat, jumping jack, sit-up, push up, etc.)(Figure 5). In other word, their total high intensity works out time was 14 minutes and recovery time for 16 minutes.

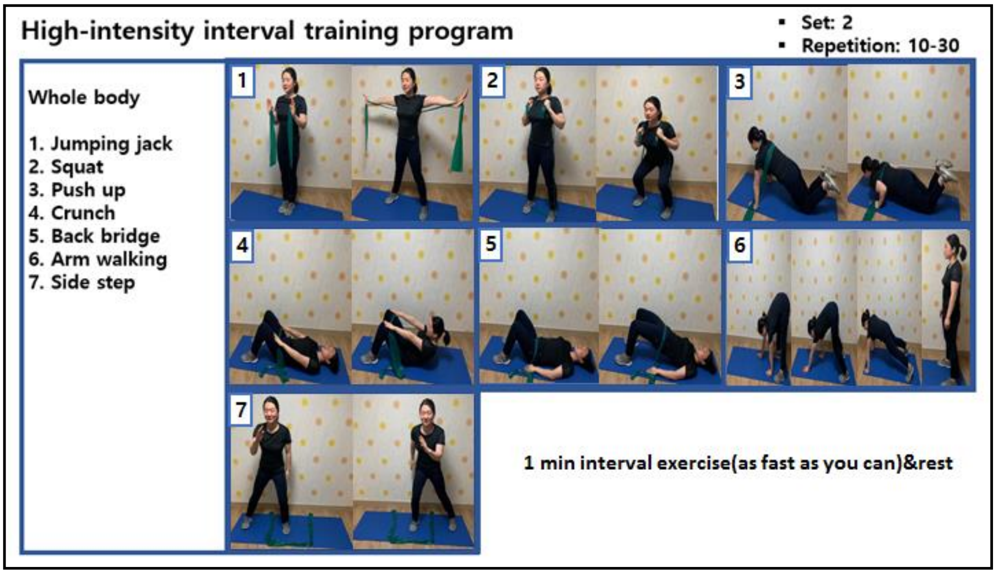

Figure 5. Exercise program for high intensity interval training group

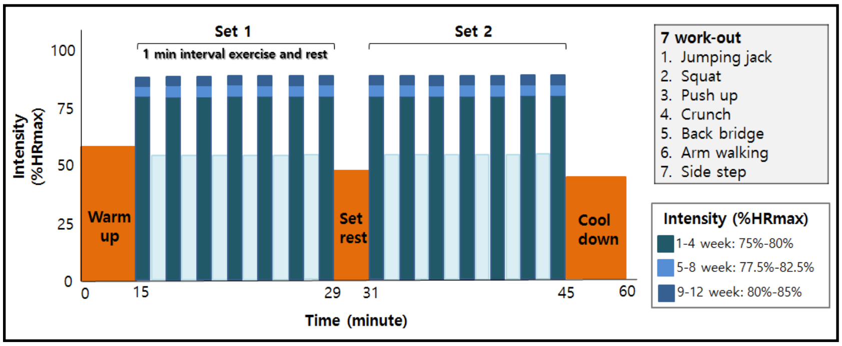

Figure 6. High−intensity interval training intensity protocol

Heart rate was monitored individually so that patients can control their heart rate in every session. When their heart rate exceeds to targeting heart rate, patients were instructed to stop their work out and slowly walk in place. Exercise intensity was gradually increased from 75% to 85% HRmax, and RPE from 14 to 17 every 4 weeks (Figure 6). Average of patients' heart rate was observed 77.4% at 1 to 4 weeks, 80.9% at 5 to 8 weeks and 82.7% 9 to 12 weeks (Figure 7).

Figure 7. Heart rate monitored for high intensity interval training

3.2 Moderate−Intensity Continuous Training Program

Home based moderate intensity interval training program consist of 60 minutes that takes 30 minutes each for walking and resistance exercise twice a week for 12 weeks (Figure 8). Exercise intensity was set to RPE 12 to 15. Waking was recommended to exercise at ‘somewhat hard’ and resistance exercise was instructed to follow the exercise program broacher. Patients in moderate intensity interval training group received exercise education at center at the beginning and in the middle of the intervention in order to do walking and resistance exercise at home (Figure 9). They were provided green and blue color resistance band to increase exercise intensity steadily. The amount of the exercise was monitored by pedometer record and daily log file (Figure 10).

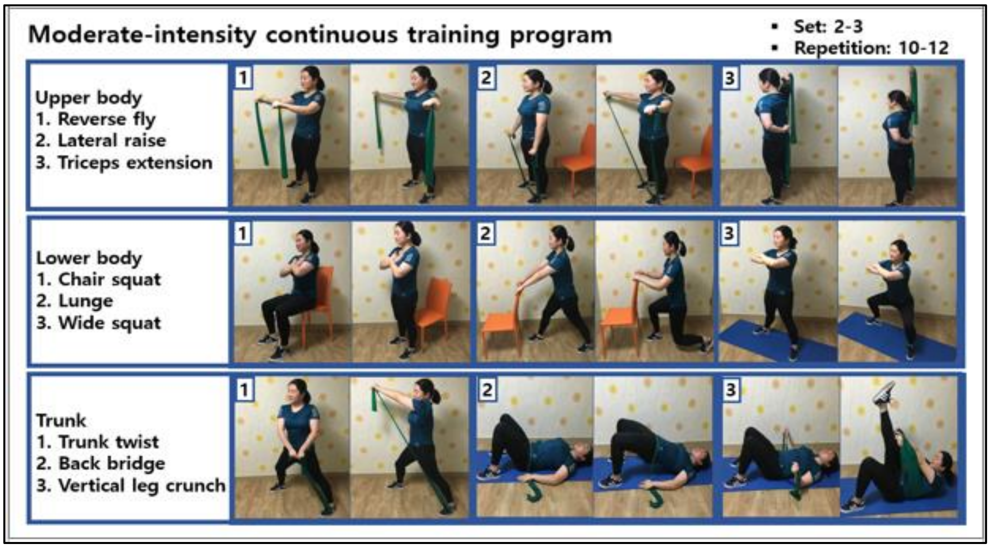

Figure 8. Exercise program for moderate−intensity continuous training group

Figure 9. Exercise education for moderate intensity continuous training group at 0 week, 6-week

Figure 10. Pedometer, resistance band, daily log file for moderate intensity continuous training group

4. Measurements

Four well-trained examiners help the patients' pre- and post-test. The measurement variables and methods of this study are as follows (Table 3).

Table 3. Measurements

Variables	Method	Model & Manufactory
Blood pressure -SBP/DBP	Blood pressure	BPBIO-320s
Body Composition -Fat mass -Lean mass -Bone mineral density	DXA(dual-energy X-ray absorptiometry)	Hologic Discovery W
Muscle Strength -Upper body strength and endurance -Lower body strength and endurance	-Grip strength -Arm curl -Cybex -Chair stand	-My-5402, TAKEI -Senior fitness test - HUMAC NORM system, CSMI - Senior fitness test
Physical fitness -Cardiovacular endurance -flexibility -Agility&balance	6 min walk Chair sit& reach Back scratch Time up & go	Senior fitness test
Quality of life, Physical activity	Self reported questionnairs	FACIT-P K-PASE

4.1 Body Composition and Bone Mineral Density

Dual energy x-ray absorptiometry (DXA, Hologic Discovery W, Waltham, MA, USA) which uses two different low level of X-ray was used to estimate bone mineral density and body composition. Researcher let the patient remove all objects (e.g., wallet, cell phones, jewelry) from their body, and make them lying straight on the scan table. After adjusting the position so that patient is in the center of the table with respect to the center lines at the head and foot of the pad, whole body scan was taken for 6 minutes in a fixed position (Figure 11).

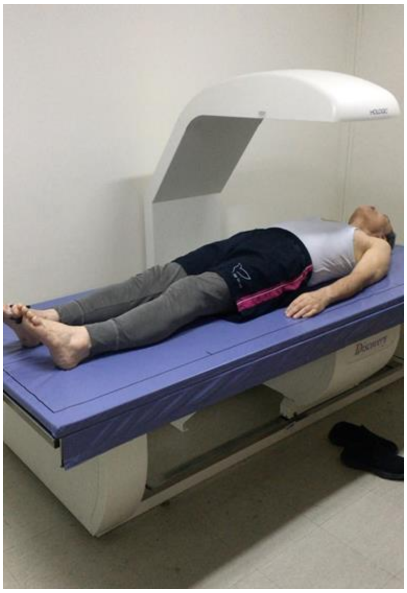

Figure 11. DXA scanning

4.2 Muscle Function

4.2.1 Grip Strength

Measurement of hand grip strength is a simple and non-invasive marker of muscle extremities, therefore, hand grip dynamometer (Takei, Grip D, T.K.K. 5401; Niigata City, Japan) was used to estimate upper body muscle strength. Researcher adjusted the grip size as the patient's proximal and middle phalangeal joint is at a 90° angle on the handle. Patient was asked to make their elbow straight and 15° abduction of glenohumeral joint so that neither hand nor dynamometer touch the body. Lastly, researcher check whether patient's head is straight and looking forward, the feet are hip width apart and even in a standing position. After finishing the practice trial at a submaximal power, patients were instructed to squeeze the hand grip maximally for 3 seconds. The grip strength was measured twice in each hand with alternating. And the average of these values was used as data (Figure 12).

Figure 12. Grip strength test

4.2.2 Arm Curl

Arm curl test which is part of the Senior Fitness Test(SFT) was conducted to evaluate functional fitness of upper body muscle endurance. The test was performed on patient's dominant arm side in seated position. Patient holding the 4kg dumbbell in the hand in a vertically down position beside the chair. In elbow flexion phase, patient curls the arm up through a full range of motion with hand supination. And then, gradually return to starting position in elbow extension phase. Repeat two phases as maximally for 30 seconds. The total number of biceps curl was recorded. Before the test, researcher make sure patient is aware of the correct posture and give attention to prevent injury from incorrect movement such as elbow hyperextension (Figure 13).

Figure 13. Arm curl test

4.2.3 Isokinetic Strength and Endurance

To evaluate muscle strength, peak torque was measured by 5 times of knee extension and flexion with participants' dominant leg at an angular velocity of 60° /sec. Muscle endurance was assessed by total work done of 15 times at an angular velocity of 180° /sec. Fixed parameters were chair back angle and chair rotation angle which was set to 85° , 40° each. And the dynamometer height and rotation angle was fixed to 8, 40° each. Monorail scale and chair seat fore/afterward position was basically set to 38, however, setting value were variable depending on the patient's physical characteristics so that the axis of the dynamometer line up with the lateral epicondyle. Knee extension range of motion was set to −5° and flexion range of motion was set to 95. Before the test base−line exam was conducted with 4 to 5 repetition at 50% effort considering that most of patients have no experience on isokinetic measurement. During the test researcher keep encouraging patient so that patient can reach to best performance. After sufficient recovery time, the isokinetic muscle endurance test carried out in the same way (Figure 14).

Figure 14. Isokinetic strength test

4.2.4 Chair Stand

30 seconds of chair stand test which is also part of the Senior Fitness Test(SFT) was performed additionally to evaluate lower body muscle endurance. Briefly, patient was instructed to sit in the middle of the chair and place their hand on the opposite shoulder crossed. When researcher give a sign to start the test, patient repeated full standing and sit back down motion as many as possible until hearing the stop sign. Researcher advise patient not to use recoil to stand up and make the knee joint is straightened when they stand up. Number of sit and stand times was recorded to use as a data. The test was performed with a seat height of 45cm with no arm regardless of the height of the patient. Chair was placed back of a wall to prevent movement during the test (Figure 15).

Figure 15. Chair stand test

4.3 Physical Function

4.3.1 6-minute Walk

6 minutes walk was performed to evaluated cardiovascular ability. Two cones were placed in a straight line with 25m distance. The patient repeats walking around 50 meter course for 6 minutes at a fast pace. Researcher noticed the patient be careful not to run ans checked whether both feet didn’t fakk frin tge ground at the same time. The patients walking distance was recorded in meters (Figure 17).

4.3.2 Chair Sit & Reach

Chair sit and reach was performed to evaluated flexibility. After allowing the patient to sit at the end of the chair with left leg folded at 90° degree and right leg is stretched. Let the right heal touch the ground and explain that the subject should be able to get close to his right foot by overlapping his upper body. The distance between the toe and fingertip was measured (Figure 17).

4.3.3 Back Scratch

Back scratch was performed to evalutated shoulder mobility. After making the subject in a straight posture, the right arm is extended up to the back and the left arm is stretched backward from the downward direction. The fingertip distance is measured in the maximum range of motion of the shoulder joint. so that the distance between the two hands is as close as possible (Figure 17).

4.3.4 Time Up & Go

Time up & go was performed to evaluate motor ability. After placing the subject in a chair, measure the time until the cone in front of 2.44 m turns fast and sit back. At the beginning of the measurement, make sure the subject is sitting tightly on his back. Avoid running both arms apart from the ground during measurement (Figure 17).

Figure 17. Senior fitness test

4.4 Self-reported questionnaire–FACT–P/ K–PASE

Two types of questionnaires were utilized to qualitatively assess patients' quality of life and physical activity. Multidimensional FACT–P(functional assessment of cancer therapy–prostate) assessed quality of patient's life using 27 core items in four domains; Physical, Social/Family, Emotional and Functional well–being. Additionally, 12 specific items for prostate related symptoms were included. The questionnaire composed of Likert–type scale, total score is ranged from 0 to 156. The higher score indicates the higher quality of life.

K–PASE (Korean version of physical activity scale for elderly) were used to assess physical activity with 10 items (6 items for leisure time activity, 3 items for household activity, 1 item for work–related activity). Weight was assigned based on activity type and frequency of activity. Score range from 0 to 360 , higher scores indicate more physical activity (Figure 18).

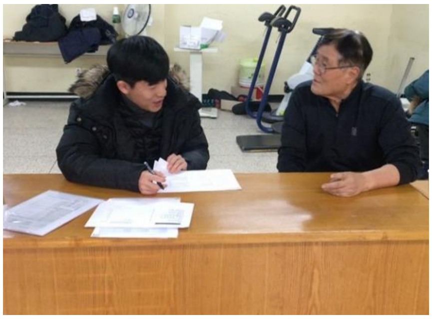

Figure 18. Questionnaire survey

5. Data Analysis

Results are presented as means ± standard deviation calculated using descriptive statistics. P−values were two sided, with $p < 0.05$ considered statistically significant. The normal distribution was confirmed through the normalization test of two independent groups. T−test was performed to examine the difference of the results among groups in age, height, body weight, lean mass, fat mass, BMI and blood pressure. Two−way ANOVA with repeated measures was performed to verify the interaction effect between group and time. Statistical analysis was performed using SPSS version 23.0 (SPSS, Chicago, IL).

Ⅳ. Results

1. Baseline Characteristics of Participants

Independent T-test was performed to examine the difference between the differences between the groups. Pre-measured values in all variables were not statistically significant between groups(p>.05)(table 4).

Table 4. Baseline clinical characteristics of participants

Variable	High-intensity interval training group (n=9)	Moderate-intensity continuous group (n=9)	*p*-value
Age (years)	72.78±4.05	76.00±4.09	.947
Height (cm)	165.50±11.09	164.04±8.14	.795
Weight (kg)	68.47±8.23	61.01±7.49	.846
Lean mass(g)	45898.47±5775.64	41734.95±3809.67	.090
Fat mass(g)	20242.71±4500.44	17228.56±5282.65	.211
BMI(kg/m2)	26.07±1.52	23.78±3.00	.580
SBP(mmHg)	129.44±15.29	126.44±17.96	.708
DBP(mmHg)	75.00±10.85	67.00±8.57	.102
Gleason score(score)	7.66±1.11	7.44±1.13	.222
Previous proctectomy(n)	3	0	
Cancer stage(n)			
localized	6	8	
advanced	3	1	

*HIIT=high intensity interval training, MICT=moderate intensity continuous training, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure. D*ata presented as mean ± SD.

Blood data which were measured before participating in the exercise program were analyzed. Independent T−test was performed to examine the difference between the differences between the groups. Pre−measured values in all variables were not statistically significant between groups ($p>.05$). The two groups were not statistically different (table 5).

Table 5. Blood markers absolute values

Variable (HIIT,MICT)	High−intensity interval training group	Moderate−intensity continuous group	*p*−value
PSA (ng/ml) (n=8,7)	6.39±14.71	1.36±1.86	.444
Testosterone (ng/ml) (n=8,7)	0.14±0.21	1.61±2.59	.185
Hb (g/dL) (n=9,9)	13.87±0.62	13.68±1.47	.730
Cholesterol (mg/dL) (n=9,9)	177.44±39.55	158.22±36.27	.299
LDL (mg/dL) (n=8,6)	98.12±41.35	81.16±24.93	.393
HDL (mg/dL) (n=8,6)	49.62±9.99	44.50±10.29	.371
TG (mg/dL) (n=8,5)	154.00±49.30	113.20±45.92	.165
GOT (mg/dL) (n=9,9)	35.77±14.66	27.88±7.02	.165
GPT (mg/dL) (n=9,9)	44.77±34.24	23.33±9.02	.088

HIIT=high intensity interval training, MICT=moderate intensity continuous training, PSA= prostate specific antigen, LDL=low density lipoprotein, HDL−high density lipoprotein, TG=triglycerides, GOT= glutamic oxaloacetic transaminase, GPT= glutamic−pyruvic transaminase, Data presented as mean ± SD.

2. Change of body composition and bone mineral density

The body composition and bone mineral density was analyzed via DXA scan. The result showed that there was no statistically significant difference of interaction between group and time on all body composition and bone mineral density−related variables (table 6).

Table 6. Change of body composition and bone mineral density

Variable	Group	Pre	Post	F	time* group
Body composition					
Whole body total mass (kg)	HIIT	68.47±8.23	70.36±8.73	3.687	.091
	MICT	61.01±7.49	61.88±6.91		
Whole body lean mass (kg)	HIIT	45.89±5.77	45.28±5.11	0.045	.838
	MICT	41.73±3.80	40.69±3.79		
Whole body fat mass (kg)	HIIT	20.24±4.50	22.76±4.81	0.584	.467
	MICT	17.22±5.28	19.11±5.46		
Whole body percentage fat (%)	HIIT	29.48±4.52	32.15±4.01	0.326	.583
	MICT	27.76±6.37	30.50±6.63		
Bone mineral density					
Whole body BMD (g/cm^2)	HIIT	1.12±0.10	1.11±0.10	0.003	.964
	MICT	1.06±0.15	1.06±0.15		
T−score (score)	HIIT	−0.76±1.07	−0.81±1.10		
	MICT	−1.52±1.81	−1.46±1.76	0.766	.407

HIIT, high−intensity interval training(n=9); MICT, moderate−intensity continuous training(n=9); BMD, bone mineral density. Data presented as mean ± SD.

3. Change of muscle function

3.1 Upper body muscle strength and endurance

Muscle function of upper and lower body were separately assessed to define the effects of 12 weeks exercise intervention. There was significant difference of interaction between group and time in arm curl which was measured for upper body muscle endurance(p=.019). When the change was observed over the time, there was a significant improvement in grip strength(p=.021) and arm curl(p<.001)(Table 7).

Table 7. Change of upper body muscle strength and endurance

Variable	Group	Pre	Post	F	time	time* group
Upper body muscle strength						
Grip strength (kg)						
	HIIT	34.18±3.54	36.12±4.69	0.044	.021*	.837
	MICT	28.91±7.15	30.63±6.44			
Upper body muscle endurance						
Arm curl (counts/ 30 sec)						
	HIIT	17.44±1.87	22.11±2.71	6.780	<.001***	.019*
	MICT	13.77±6.11	15.11±6.80			

*HIIT, high-intensity interval training(n=9); MICT, moderate-intensity continuous training(n=9); Data presented as mean ± SD, *p<0.05, ***p<0.001.*

3.2 Lower body muscle strength and endurance

The relative isokinetic muscle strength and endurance value were presented by dividing each peak torque by percentage of body weight. There was significant difference of interaction between group and time in knee extensor at an angular velocity of 180°/sec(p=.035). Also, chair stand was significantly improved in HIIT over time and group(p=.012). There was no significant interaction in isokinetic test at 60°/sec, however, both knee extensor(p=.036) and knee flexor(p<.001) peak torque improved over time(Table 8).

Table 8. Change of lower body muscle strength and endurance

Variable	Group	Pre	Post	F	time	time* group
Lower body muscle strength						
Isokinetic 60°/sec peak torque/ %BW (Nm)						
Knee extensor						
	HIIT	149.66±29.91	157.33±20.38	.048	.036*	.830
	MICT	118.33±26.57	124.66±20.53			
Knee flexor						
	HIIT	45.33±21.50	77.11±18.79	<.001	<.001***	.987
	MICT	35.22±14.49	66.88±7.95			
Lower body muscle endurance						
Isokinetic 180°/sec peak torque/ %BW (Nm)						
Knee extensor						
	HIIT	97.33±15.78	117.77±27.37	5.280	.001**	.035*
	MICT	78.66±21.27	84.11±18.59			
Knee flexor						
	HIIT	44.66±18.88	56.22±14.13	1.880	<.001***	.189
	MICT	38.33±13.22	43.33±10.18			
Chair stand (counts/ 30 sec)						
	HIIT	15.55±2.78	23.44±3.77	8.072	<.001***	.012*
	MICT	13.66±3.27	15.77±5.86			

*HIIT, high-intensity interval training(n=9); MICT, moderate-intensity continuous training(n=9); Data presented as mean ± SD, *p<0.05, **p<0.01, ***p<0.001*

4. Change of Senior Fitness Test

There was significant difference of interaction between group and time in arm curl which was measured for upper body muscle endurance(p=.019). When the change was observed over the time, there was a significant improvement in grip strength(p=.021) and arm curl(p<.001)(Table 9).

Table 9. Change of Senior Fitness test

Variable	Group	Pre	Post	F	time	time* group
Sit& reach (cm)	HIIT MICT	−0.75±11.64 −7.62±13.86	4.88±8.86 −3.61±14.97	.064	.155	.804
Back scratch (cm)	HIIT MICT	−18.16±7.22 −32.82±14.01	−13.57±6.98 −29.00±16.48	.037	.051	.850
TUG (sec)	HIIT MICT	5.32±0.43 6.62±1.51	5.13±0.45 6.12±1.47	4.747	<.001 ***	.045*
6min walk (m/6min)	HIIT MICT	569.77±32.47 455.44± 112.55	579.11±65.95 490.88± 110.90	1.667	.042*	.215

*HIIT, high−intensity interval training(n=9); MICT, moderate−intensity continuous training(n=9); TUG, time up and go; Data presented as mean ± SD, *p<0.05, **p<0.01, ***p<0.001.*

5. Change of quality of life and physical activity

There was significant difference of interaction between group and time in FACT−P(p=.019) which was surveyed for health−related quality of life. In physical activity questionnaire, no statistical change was found; however, there was visible increase in moderate intensity continuous group (Table 10).

Table 10. Change of Self−reported outcomes of physical activity and quality of life

Variable	Group	Pre	Post	F	time	time*group
K-PASE (score)	HIIT	144.76±73.66	141.10±50.73	2.538	.209	.131
	MICT	103.51±47.74	140.99±36.34			
FACT-P (score)	HIIT	109.55±12.82	120.55±8.58	8.273	.127	.011*
	MICT	99.44±25.67	96.33±23.50			

*HIIT, high−intensity interval training(n=9); MICT, moderate−intensity continuous training(n=9); K−PASE, Korean version of physical activity scale for elderly; FACT−P, functional assessment of cancer therapy−prostate. Data presented as mean ± SD, *p<0.05*

V. Discussion

Recent meta-analyses indicate that energy expenditure improves health-related quality of life by enhancing cardiorespiratory and metabolic fitness in cancer patients(Ferrer, Huedo-Medina, Johnson, Ryan, & Pescatello, 2010; Speck, Courneya, Mâsse, Duval, & Schmitz, 2010). To replace low-intensity exercise, various attempts have begun to increase energy expenditure (Schmitt et al., 2016; Stefanelli et al., 2013). Repeated short bout of high-intensity exercise interspersed with recovery periods referred to as high-intensity interval training has been proved to be safe and effective in reducing general(Gibala, Little, MacDonald, & Hawley, 2012a; Weston, Wisløff, & Coombes, 2014b). Effects of high intensity interval training were investigated in colorectal, lung, breast cancer patients, however, to our knowledge this is the first trial that intervene in prostate cancer patients receiving androgen deprivation therapy.

The major findings in the present study were that 12 weeks of either high or moderate intensity exercise clearly demonstrated effects on physical fitness including muscle strength, muscle endurance, cardiorespiratory endurance, motor ability and health related quality of life. Especially, high intensity interval training showed statistically greater improvement on upper and lower body muscle endurance and health related quality of life than moderate intensity continuous training. In one cross-sectional study, patient with prostate cancer undertaking hormone suppression, as expected, had significantly lower whole body bone mineral density higher percent of body fat than age-matched healthy elderly. And, they consistently impaired physical and functional musculoskeletal performance (D. Galvao et al., 2009b). Thus, maintaining physical fitness is very important for the elderly. It not only enables daily life, but also protects against falls, sarcopenia and chronic diseases which make available to prolong healthy life years(Courneya et al., 2003). Therefore, our study is a significant finding considering that high intensity interval training showed great effect on improving upper- and lower body muscle endurance. As with other studies, our findings also suggest that high intensity interval training increases perception of health related quality of life (Knowles, Herbert, Easton, Sculthorpe, & Grace, 2015). This type of exercise can be perceived to be more enjoyable and motivate than other exercise type(Bartlett et al., 2011). There is no reason not to do high intensity interval training if the patients can get similar or better benefits.

Although patients were encouraged to do high or moderate intensity exercise twice a week for 12 weeks, the effects of both types of exercise were not shown significant improvement in body composition and bone mineral density in whole body DXA. In previous studies, we can find that some of studies have improved body composition and some are not(Yunfeng, Weiyang, Xueyang, Yilong, & Xin, 2017). We can assume that there is a limitation to improve body composition and bone mineral density because of negative effects of androgen deprivation therapy. And also, we could not control their life style including diet.

In some point of views, some people are concern about exercise may trigger tumor cell growth. Yet the mechanisms of tumor growth protection are not clarified, exercise, epinephrine and IL-6 to NK cell mobilization and activation, and ultimately to improved control of tumor growth(Pedersen et al., 2016). Also, regulation systemic factors such as sex hormones, metabolic hormones, cytokines, and immune function has suggested as candidate mechanisms linking exercise to cancer protection (Verma, Singh, Singh, Singh, & immunotoxicology, 2009). Follow up studies are needed because exercise may be dangerous to cancer patients who have metastasized, and it is necessary to discuss exercise methods according to cancer patient's diverse condition. In this study, no side effects of high intense exercise were found, but more subjects were required to be validated.

The purpose of this study was to compare the effects between high intensity interval training and moderate continuous training. Therefore, ideal method to conform the effects is to make the environment the same except for the exercise intensity. However, subjects were cancer patient and due to the constraints of the given environment we could not supervised all group. The compliance rate for exercise was calculated as the date of attendance for high intensity interval training group, and the compliance rate was 87.8%. In the case of moderate intensity continuous training group, the compliance rate was 89.8% which was calculated based on data recorded in a daily log file. Patients with an attendance rate of less than 70% were 3 in each group, and they were excluded from the data analysis. Although there is a similarity between the two groups, there is a limitation in that an accurate comparison cannot be made because the calculating method of the compliance rate was different.

There are some limitations in this study. Because of the IRB we could not able to assign control group. Since the subjects of the study were given priority to choose the exercise group, randomized control trial is not made. Also, due to limitations of the research environment, sample size was insufficient. In order to generalize the results of the study, follow-up studies in which the control group is set, the sample number should be lager, and randomized control trial should be conducted. Also, further studies are needed to quantitatively measure the energy expenditure in the exercise program and to compare the effects of exercise intensity. To improve body composition and muscle strength it is necessary to consider exercise duration, frequency and intensity, time, type.

Ⅵ. Conclusion

In conclusion, high–intensity interval exercise positively affects the improvement of muscular function, especially in the upper extremities and lower extremities and has a positive impact on improving health–related quality of life in patients with prostate cancer receiving ADT. Both 12–week of high intensity interval exercise and moderate intensity continuous exercise have a positive effect on prevention of significant decline in body composition and bone mineral density. Two types of exercise show similar effectiveness across cardiorespiratory endurance and improvement of power suggesting that high intensity interval exercise may be a time–efficient component of program.

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국 문 초 록

서론:

안드로겐 박탈 치료를 받은 후 전립선 암 환자의 대다수는 신체 조성 및 신체 기능에서 부정적인 변화를 경험한다. 이로 인해, 대사 증후군 및 만성 질환에 걸릴 수 있는 위험이 증가하여 환자의 건강 관련 삶의 질을 저하시키고, 이차적 요인으로 인한 사망률을 높인다. 운동은 이러한 부작용을 완화시키는데 긍정적인 영향을 주는 것으로 알려졌으며, 전립선암환자에서 수 많은 운동 중재 연구가 이루어져왔다. 그러나, 전립선 암환자에게 더 효과적일 수 있는 고강도 인터벌 운동의 효과를 하는 연구는 부족한 실정이다. 따라서, 본 연구의 목적은 고강도 인터벌 운동이 전립선 암 환자의 근 기능과 신체조성 변화에서 미치는 영향을 중등도 지속 운동과 비교하여 규명해 보고자 한다.

연구방법:

연구참여기준을 충족시킨 24 명의 암환자가 모집되어, 고강도 인터벌 운동군(n=12) 또는 중강도 지속 운동군(n=12)으로 할당되었다. 모든 암환자는 운동프로그램의 사전/사후에 (1) 신체조성과 골밀도, (2) 근력 및 지구력, (3) 노인체력, (4) 삶의 질, 신체활동량 관련 설문지를 측정하였다. 두 그룹의 운동 유형은 저항성 밴드를 이용한 복합운동으로 하였다. 고강도 인터벌 그룹은 주당 2회 운동을 실시 하였으며, 최대 심박수의 75-85%와 운동자각도 14-17을 목표로 이루어졌다. 중강도 지속 운동군에서는 운동자각도 12-15를 목표로 걷기와 근력운동을 하기 위해 두 번의 운동교육을 받았으며, 운동량은 만보계 기록과 로그파일을 통해 확인하였다.

연구결과:

12주 운동프로그램에서 전립선 암 환자 18명(고강도 인터벌 운동군, n=9; 중강도 지속 운동군, n = 9)이 참여를 완료하였고, 6명의 환자가 다음과 같은 사유로 중도 탈락하였다(통증호소, n=2; 병원이동, n=2; 개인사유, n=2). 고강도 인터벌 운동군에서 상지 근지구력 평가를 위한 Arm curl test(p = .019)와 하지 근지구력 평가를 위한 각 속도 180° /초에서의 등속성 운동검사(p = .035) 및 Chair stand test (p = .012)에서 유의한 증가를 보였다. 또한, 삶의 질을 평가하는 설문지인 FACT-P의 점수가 고강도 인터벌 운동군에서 10% 이상 증가하여, 유의한 차이를 보였다(p = .011). 그러나, 신체조성, 골밀도, 근력에서 그룹시기간 유의한 차이는 나타나지 않았다.

결론:

12 주간의 고강도 인터벌 운동은 안드로겐 박탈 치료를 받는 전립선 암 환자의 상, 하체 근지구력과 삶의 질을 향상시키는데 그룹시기간 유의한 차이가 나타났다. 이외에 변인은 중강도 지속 운동과 유사했기 때문에 고강도 인터벌 운동은 시간 대비 효율적인 운동 전략이 될 수 있다. 후속 연구로 전립선 암 환자의 신체조성, 골밀도 그리고 근력을 포함한 건강관련 체력을 개선하기 위한 운동중재연구가 필요하다.

주요어: 고강도 인터벌 운동, 전립선암, 안드로겐 박탈치료, 신체조성, 근기능

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